REMARKS

In response to the Office Action dated July 31, 2003, Applicants request entry of the foregoing amendments and consideration of the following remarks.

Upon entry of the present amendment, claims 5, 13, and 18 will be cancelled and new claims 50-101 added, leaving claims 1-4, 6-12, 14-17, and 19-101 pending; of those, claims 6-8, 19-35, and 38-49 were withdrawn from consideration by the Examiner after Restriction. Thus, claims 1-4, 9-12, 14-17, 36-37, and 50-101 are presently under consideration. Claims 1, 3, and 4 are amended to remove reference to the mouse sequences, SEQ ID NOs:1 and 2. Claim 1 has been additionally amended to remove a recitation of a fragment. Claim 2 has been amended to recite a fragment of SEQ ID NO:8, the fragment being at least 10% of the length of SEQ ID NO:8; support for this amendment can be found at p. 21, ¶¶53-55, *inter alia*. Claim 3 has been additionally amended to recite nucleotides 80 to 676 of SEQ ID NO:7, and to remove a reference to fragments; support for this amendment can be found at p. 10, ¶30, p. 17, ¶43, and the sequence listing, *inter alia*. Claim 4 has been additionally amended to recite a nucleic acid complementary to nucleotides 80 to 676 of SEQ ID NO:7; support for this amendment can be found at pp. 9-15, ¶30, *inter alia*. Claims 36 and 37 were amended in response to the Examiner's species election requirement. Additionally, claim 36 was amended to recapture elected subject matter (nucleic acids comprising SEQ ID NO:9) from claim 34 that was erroneously withdrawn by the Examiner; and to include the limitation "full length;" support for this amendment can be found in the claims as filed and at p. 73, ¶339, *inter alia*. Claim 37 was amended to recite nucleic acids over 20 bases that hybridize to a probe consisting of (a) nucleotides 1 to 1118 of SEQ ID NO: 9 or (b) a sequence complementary to nucleotides 1 to 1118 of SEQ ID NO: 9, in 0.9% NaCl at 75°C. Support for these amendments can be found at, p. 73, ¶339, pp. 19-20, ¶¶ 45-47, and the claims as filed, *inter alia*.

Support for new claims 50-101 can be found throughout the specification, for example at pp.45-46, ¶¶ 174-177; the sequence listing SEQ ID NO:7; p. 16, ¶34, pp. 19-20, ¶¶ 45-50; pp. 29-34, ¶¶ 85-119; pp. 21-22, ¶¶ 53-55; pp. 73-74, ¶ 339; and original claims 1-3, 5, 9-18, and 38, *inter alia*. No new matter has been added.

The Examiner further objected to the language of the specification, and required a substitute specification in proper idiomatic English. The Applicants herewith submit such a substitute specification in compliance with 37 CFR 1.52(a) and (b) and 1.125; both a clean copy and a marked-up copy showing the changes made are enclosed. No new matter is added by the amendments to the specification incorporated therein; thus the substitute specification contains no new matter. The title is amended to omit the word "Novel," as requested by the Examiner.

Objections to the Claims

The Examiner objected to claims 1-5, 9-18, 36 and 37 for "reciting polynucleotides, vectors, and host cells not encompassed by the elected invention." Applicants elected Group II, relating to nucleic acids encoding human AID, vectors, and host cells. Claims 5, 13, and 18 are canceled by the present amendment. Claims 1-4 are amended to remove reference to the mouse sequences, SEQ ID NOs:1 and 2. As amended, dependent claims 9-12 and 14-17 no longer refer to non-elected inventions or species. Applicants protest the Examiner's requirement that claims 36 and 37 be amended to remove subject matter relating to non-elected species. Claims 36 and 37 have been amended to remove reference to non-elected species, which amendment has been made to in order to make a full response to the Office Action; however, Applicants hereby request examination of the non-elected species immediately upon a determination that the species elected is patentable, even though those non-elected species no longer appear in the claims. In any case, Applicants reserve the right to rejoin the subject matter deleted by this amendment.

Claim Rejections under 35 USC §112, ¶2

The Examiner rejected claims 1, 2, 9, 10, 14, and 15 as "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." (Office Action, pp. 3-4) Claim 1 was rejected for the use of the term "functional fragment," as, according to the Examiner, "it is not clear whether the 'functional fragment' recited is a fragment of the nucleic acid molecule or the protein set forth by SEQ ID NO: 8. In addition, it is not clear what specific function of the 'functional fragment' the applicants are

intending to recited, for example, enzymatic activity, substrate binding, cofactor binding, immunogenicity and so forth." (Office Action, p. 4)

Claim 1 has been amended to remove the term "functional fragment," thus obviating this rejection and the rejection of claims 9, 12, 14, and 15, which are dependent from claim 1. Amended claim 2, now in independent form, recites: "An isolated nucleic acid encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8, wherein the fragment has a cytidine deaminase activity." As the claim is thus limited to those fragments having "a cytidine deaminase activity," applicants submit that it is not indefinite.

According to the Office Action on page 4, "Claim 3 is confusing and has two interpretations. It is not clear whether claim 3 is reciting SEQ ID NO: 7 and any nucleic acid comprising a fragment of SEQ ID NO: 7 or SEQ ID NO: 7 and any nucleic acid comprising SEQ ID NO: 7."

Claim 3 has been amended to recite: "An isolated nucleic acid comprising the nucleotide sequence of nucleotides 80 to 676 of SEQ ID NO:7, or a fragment comprising a sequence of over 20 continuous bases of nucleotides 80 to 676 of SEQ ID NO:7." Applicants respectfully submit that this claim, as amended, is clearly reciting the coding region of SEQ ID NO:7 (nucleotides 80 to 676 of SEQ ID NO:7 represent the coding region: see, e.g., the Sequence Listing) and fragments of the coding region of SEQ ID NO:7, wherein the fragments comprise over 20 continuous bases. Applicants respectfully submit that this language is not indefinite.

Claims 5, 13 and 18 were rejected by the Examiner as indefinite due to the recitation of "hybridizes under stringent conditions." (Office Action, p. 4) Claims 5, 13 and 18 have all been cancelled, thus obviating this rejection.

Finally, claim 36 was rejected as indefinite for allegedly having two interpretations: "Claim 36 could be meant to recite a polynucleotide comprising the full-length complement of SEQ ID NO:9. Alternatively, Claim 36 could be meant to recite a polynucleotide of any length that is complementary to any length of SEQ ID NO: 9." Claim 36 has been amended to recite "the full length of SEQ ID NO:9."

For the foregoing reasons, Applicants respectfully request that the rejections under 35 USC §112, ¶2 be withdrawn.

Claim Rejections Under 35 USC §112, ¶1

Claims 1-3, 5, 9-11, 13-16, 18, 36, and 37 were rejected under 35 USC § 112, first paragraph:

> because the specification, while being enabling for the polynucleotides of SEQ ID NO:7 and polynucleotides encoding SEQ ID NO:8, does not reasonably provide enablement for any fragment of the polynucleotide set forth by SEQ ID NO:7, any fragment of a polynucleotide that hybridizes under stringent conditions to SEQ ID NO:7, the nucleic acid of SEQ ID NO:9, any polynucleotide of any length that is complementary to any length of SEQ ID NO:9, or any polynucleotide that encodes a fragment of SEQ ID NO:8.

(Office Action, p. 5) The Examiner asserts that "Claim 1 is so broad as to encompass any polynucleotide sequence that encodes a peptide fragment of SEQ ID NO: 8" (Office Action, p.6). Claim 1, as amended, is limited to nucleic acids encoding a protein comprising the amino acid sequence of SEQ ID NO:8 (all mention of fragments having been deleted). The Examiner has acknowledged that the specification is enabling for such a nucleic acid.

The Examiner further states that "Claim 2 is so broad as to encompass any polynucleotide sequence that encodes a peptide fragment of a protein that is a peptide fragment of SEQ ID NO:8." (Office Action, p.6). Claim 2 as amended recites nucleic acids encoding a polypeptide comprising a fragment of SEQ ID NO:8, the fragment being at least 10% of the length of the amino acid sequence of SEQ ID NO:8, wherein the polypeptide has a cytidine deaminase activity. The full sequence of SEQ ID NO:8 is, of course, included in the specification. Furthermore, regions likely to be involved in the recited cytidine deaminase activity are described in the specification in detail, including the cytidine/deoxycytidine deaminase motif (see, for example, Figure 5 and the discussions thereof at page 51; and see also page 59, paragraphs 237-239). It would be well within the ability of one of ordinary skill in the art to determine whether a peptide fragment of SEQ ID NO:8 comprising the cytidine/deoxycytidine deaminase motif has such activity, e.g., using methods well known in the art, including methods described in the present application, and the amount of guidance in the specification is such that

undue experimentation would not be required. Further, it would be trivial for such a person to design a nucleic acid having a sequence that encodes such an active fragment. Thus, Applicants submit that sufficient enablement is provided for claim 2 as amended.

Claim 3, the Examiner asserts, "is so broad as to encompass any polynucleotide sequence that is a fragment of SEQ ID NO:7" (see page 6 of the Office Action). Claim 3, as amended, is limited to fragments of the coding region of SEQ ID NO:7 that are over 20 continuous bases long; one of skill in the art would expend very little effort in perusing the sequence listing, finding SEQ ID NO:7, and selecting a portion of the sequence that is over 20 continuous bases long, and is suitable for a specific application.

The Examiner rejected claim 36 as "so broad as to encompass any nucleic acid comprising a sequence complementary to SEQ ID NO:9," and claim 37 as encompassing "any polynucleotide of any length that is complementary to any length of SEQ ID NO:9."

Claim 36, as amended, is drawn to SEQ ID NO:9 and sequences complementary to the full length of SEQ ID NO:9. Claim 37, as amended, is drawn to isolated nucleic acids comprising a continuous nucleotide sequence of over 20 bases that (a) hybridize to a probe consisting of nucleotides 1 to 1118 of SEQ ID NO: 9 in 0.9% NaCl at 75°C, or (b) hybridize to a probe consisting of a sequence complementary to nucleotides 1 to 1118 of SEQ ID NO: 9 in 0.9% NaCl at 75°C. The breadth of these claims is appropriate; as noted above, the full sequence of SEQ ID NO:9 is provided in the specification, and one of skill in the art would be readily able to make and use the claimed nucleic acids. The activity of any peptide derived from the nucleic acid fragments of claim 37 is irrelevant, as "activity" is not a limitation recited in the claim; these nucleic acid fragments are useful in other ways, and one of skill in the art would be able to select a fragment having a size and sequence appropriate for her specific application, whether it be PCR, e.g., to identify mutations associated with disease (see, for example, Revy et al., 2000 *Activation-induced cytidine deaminase (AID) deficiency causes the autosomal recessive form of the Hyper-IgM syndrome (HIGM2),* Cell. 102(5):565-75 (Exh. D)), or for the construction of small interfering RNAs (siRNAs) or antisense drugs, or for expression of antigenic peptides to

use in the generation of antibodies. Instructions on how to use the fragments are disclosed in the specification in detail (see, for example, ¶¶ 21-24, ¶ 26, ¶¶ 76-84, and ¶¶ 174-181).

For these reasons, Applicants respectfully submit that claims 1-3, 5, 9-11, 13-16, 18, 36, and 37 are sufficiently enabled.

> Claims 1-3, 5, 9-11, 13-16, 18, 36, and 37 are rejected under 35 USC 112, ¶1, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, has possession of the claimed invention. These claims are directed to a genus of nucleic acid molecules with either SEQ ID NO:7, fragments of SEQ ID NO:7, fragments of any polynucleotide that hybridizes under stringent conditions to SEQ ID NO:7, polynucleotides comprising a sequence complementary to SEQ ID NO:9, polynucleotides complementary to any length of SEQ ID NO:9, or polynucleotides encoding fragments of SEQ ID NO:8. (Office Action, pages 8-9)

The Examiner asserts that the specification "does not contain any disclosure of the function" of the nucleic acid molecules recited in the claims. The Examiner further states that many functionally unrelated polynucleotides and polynucleotides without function are encompassed within the scope of the claims. (Office Action, pages 8-9)

Claim 1, as amended, claims a polynucleotide encoding a polypeptide comprising SEQ ID NO:8. Claim 2, as amended, claims nucleic acids encoding a polypeptide comprising a fragment of SEQ ID NO:8, the fragment being at least 10% of the length of the amino acid sequence of SEQ ID NO:8, wherein the polypeptide has a cytidine deaminase activity. Claim 3, as amended, claims a nucleic acid comprising the nucleotide sequence of nucleotides 80 to 676 (the coding region) of SEQ ID NO:7, or a fragment comprising a sequence of over 20 continuous bases of nucleotides 80 to 676 of SEQ ID NO:7. Claims 5, 13, and 18 have been cancelled.

The Applicants submit that there is ample written description support to satisfy 35 USC 112, paragraph 1. The specification amply discloses the claimed nucleic acids and proteins: the full-length cDNA and amino acid sequences of the human AID protein, SEQ ID NOs: 7 and 8, respectively, as well as human genomic DNA containing the AID gene, SEQ ID NO: 9. It is illogical to suggest that, when an entire sequence is disclosed, fragments of that defined sequence are not "described." Unlike the situation in Regents of the University of California v. Eli Lilly

Adams et al., 1998 or Adams et al., 1993, which allegedly teach polynucleotides with 100% identity over 272 and 69 nucleotides of SEQ ID NO:9, respectively.

Claim 5 has been cancelled, rendering the rejection moot as to that claim. Claim 37 has been amended to specify that the claimed nucleic acid must comprise a sequence of over 20 nucleotides that (a) hybridizes to a probe consisting of nucleotides 1 to 1118 of SEQ ID NO: 9, in 0.9% NaCl at 75°C, or (b) hybridizes to a probe consisting of a sequence complementary to nucleotides 1 to 1118 of SEQ ID NO: 9, in 0.9% NaCl at 75°C.

The Applicants have prepared exhibits illustrating the positions of the sequences disclosed by the Adams and Strausberg references, relative to the human AID cDNA (SEQ ID NO:7), and to the genomic AID sequences of SEQ ID NOs:9, 10 and 35; the intron-exon organization is disclosed in the specification, e.g., at ¶340 and in the sequence listing. The charts are attached hereto as Exhibits A, B, and C. As illustrated by the exhibits, none of the sequences disclosed by Adams or Strausberg anticipates any of the claims. The nucleotide numbers shown on Exhibits A and B refer to the first nucleotide of each segment, e.g., the first nucleotide of each intron or exon, or the first nucleotide of the coding region or UTR (untranslated region).

The Adams sequences (Adams AQ042682 and Adams T06576 on Exhibit A, illustrated by blue highlighting (AQ042682) and bold/underlining (T06576) on Exhibit C) fall within the first intron of the AID gene (the first intron is nucleotides 1119-5514 of SEQ ID NO:9). As noted above, claim 37, as amended, is limited to nucleic acids that hybridize to a probe consisting of either (a) nucleotides 1 to 1118 of SEQ ID NO:9, in 0.9% NaCl at 75°C, or (b) a sequence complementary to nucleotides 1 to 1118 of SEQ ID NO:9, in 0.9% NaCl at 75°C. Thus, claim 37 is not anticipated by either of the Adams sequences.

The portions of SEQ ID NO: 7 that are disclosed by the Strausberg 1999 (AI016902; pink highlighting on Exhibit C), 1998 (AA954956; double underlining overlapping the pink-highlighted sequence AA954956 on Exhibit C), and 1999 (AW135547; yellow highlighting on Exhibit C) references are within the 3'-untranslated region (UTR) of the AID gene. As shown on Exhibits B and C, nucleotides 80 to 676 of SEQ ID NO: 7 correspond to the coding region of the AID gene. The coding region is shown as a thick black rectangle in Exhibit B. Strausberg's

sequences do not include any coding sequence. Therefore, Strausberg's sequences cannot anticipate claims to nucleic acids encoding a protein, e.g., the human AID protein of SEQ ID NO: 8, as recited in claim 1. Claim 3 as amended refers only to nucleotides 80 to 676 of SEQ ID NO: 7, which is the region coding for the AID protein (see, e.g., the sequence listing) and does not include any sequence disclosed by Strausberg. Claim 5 has been canceled.

Thus, Applicants respectfully request withdrawal of the rejection of claims 1, 3, and 37 under 35 USC §102.

For the foregoing reasons, Applicants believe that the pending claims are allowable and respectfully request such action.

Enclosed is a check for excess claim fees and a check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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